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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,613	03/12/2007	Masatoshi Tohata	289779US0PCT	3580
22850	7590	06/17/2010	EXAMINER	
OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, L.L.P. 1940 DUKE STREET ALEXANDRIA, VA 22314			POPA, ILEANA	
			ART UNIT	PAPER NUMBER
			1633	
			NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/578,613	Applicant(s) TOHATA ET AL.	
	Examiner ILEANA POPA	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 April 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-15 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>04/07/2010</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-7 have been amended. Claims 8-15 are new.

Claims 1-15 are pending and under examination.

2. The objections to claim 7 and the disclosure are withdrawn in response to the amendments to the claims filed on 04/07/2010.

The rejection of claims 1-4 and 7 under 35 U.S.C. 102(b) as being anticipated by Ferrari et al. (WO 03/083125) is withdrawn in response to the amendments to the claims filed on 04/07/2010. Specifically, since the applicant deleted reference to *slr* from claim 1, the claims are not longer anticipated by Ferrari et al.

Response to Arguments

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferrari et al. (WO 03/083125), in view of both Gardan et al. (Mol. Microbiol., 1997, 24: 825-837) and Hakamada et al. (Biosci. Biotechnol. Biochem., 2000, 64: 2281-2289).

Ferrari et al. teach a method of producing a secreted protein by using a recombinant *Bacillus subtilis*, wherein the recombinant *Bacillus subtilis* comprises a deletion in the *slr* gene and wherein the recombinant *Bacillus subtilis* further comprises gene encoding a heterologous protein, i.e., the gene comprises a transcription initiation region (claims 1-3, 7-9, 12, and 13) (p. 1, line 33 to p.2, line 35, p. 3, lines 3-7, p. 36, lines 21-36). The gene encoding a heterologous protein further comprises a translation initiation region and a secretion signal region (claims 3 and 4) (p. 23, lines 24-30, p. 36, lines 3-7).

Ferrari et al. do not teach deleting *rocR* or *sigL* (claims 1, 10, 11, 14, and 15). However, doing such is suggested by the prior art. For example, Ferrari et al. teach that their method could also employ a recombinant *Bacillus subtilis* comprising a deletion in the *rocA*, *rocD* or *rocF* genes (p. 2, lines 24-29). Gardan et al. teach that *rocR* or *sigL* are transcriptional activators of the *rocA*, *rocD* or *rocF* genes (Abstract, p. 825, column 2, first full paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the *Bacillus subtilis* of Ferrari et al. by deleting *rocR* or *sigL* to achieve the predictable result of inactivating the *rocA*, *rocD* or *rocF* genes and obtain a microorganism suitable for protein production.

Ferrari et al. and Gardan et al. do not specifically teach using the cellulose transcription initiation, translation initiation and secretion signal regions as set forth by SEQ ID NO: 1 (claims 5 and 6). However, SEQ ID NO: 1 was known in the prior art (see Hakamda et al., p. 2283, column 2, p. 2284, Fig. 1; see also the enclosed sequence alignment). It would have been obvious to one of skill in the art, at the time

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the invention was made, to modify the *Bacillus subtilis* of Ferrari et al. by replacing their transcription initiation, translation initiation and secretion signal regions with the cellulose transcription initiation, translation initiation and secretion signal regions to achieve the predictable result of obtaining a microorganism suitable for the production of secreted proteins.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

The applicant argues that the instant rejection is moot in view of the amendment of claim 1 since Ferrari was not relied upon for teaching deletions or knock-outs of the genes now recited by claim 1 (including *rocR* and *sigL*) which no longer include *slr*. The applicant argues that, because it does not teach deleting *rocR* or *sigL*, Ferrari is non-analogous art.

The applicant argues that Gardan did not suggest or provide a reasonable expectation of success for the invention because the skilled artisan would have expected that inactivation of *rocR* would reduce arginine import by negatively regulating arginine permeases RocCE, leading to reduced protein production due to reductions of the amino acid arginine in the cell necessary for protein synthesis. As described by Gardan (cited in rejection) and Belitsky (attached), it has been well known in the art that RocR positively regulates the *rocABC* and *rocDEF* operons, see page 825, first full paragraph and Fig. 1B of Gardan, and page 10290, left col., 2nd paragraph of Belitsky.

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It was also well known that *rocCE* are arginine permeases involved with arginine import, see page 825, first full paragraph of Gardan and Fig. 1 of Belitsky.

Similarly, *sigL* regulates *rocABC* and *rocDEF* operons, see the abstract of Gardan, and *sigL* mutants cannot grow when arginine, ornithine, isoleucine, or valine are the sole nitrogen sources, see Debarbouille et al., abstract (attached).

Second, as disclosed by Gardan and Belitsky, it was well known that *rocA*, *rocD* and *rocF* contributed to arginine metabolism, see Fig. 1A in Gardan and Fig. 1 of Belitski. RocA, RocD and RocF have been known as enzymes relating to the production of glutamate from arginine in microorganisms. Based on this well known information, one of skill in the art would have expected that inactivating *rocADF* would have reduced the conversion of arginine into glutamate and thus cause the accumulation of arginine transported into the cell by the function of arginine permease RocCE.

However, since RocR is a positive regulator of RocCE (arginine permeases), when inhibiting RocR the ordinary artisan would have expected decreased import of arginine into the cell due to inactivation of RocCE. Therefore, the ordinary artisan would have expected that the arginine level in the bacterial cell would be decreased and would not have expected the increased productivity of heterologous proteins expressed by the claimed recombinant microorganisms.

Hakamada was cited in regard to the regulation sequence, but does not disclose the elements of the invention missing from the other references.

The applicant's arguments are acknowledged; however, the rejection is maintained for the following reasons:

Just because Ferrari does not teach deleting *rocR* or *sigL* does not mean that the rejection is moot or that Ferrari is not analogous art. First, the applicant is reminded that this is an obviousness-type and not anticipation rejection; therefore, Ferrari does not have to teach each and every claim limitation. Second, Ferrari is analogous art because it pertains to the field of applicant's endeavor, i.e., protein production by using a genetically-modified *Bacillus subtilis*.

The argument that one of skill in the art would have expected reduced protein synthesis by inactivating *rocR* or *sigL* is not found persuasive. The evidence provided by the applicant only indicates that, because arginine is not imported into the *B. subtilis* cells, the *B. subtilis* having inactivated *rocR* or *sigL* cannot grow when either of the arginine, ornithine, isoleucine, or valine is used as a nitrogen source. In other words, RocCE are only necessary when any of arginine, ornithine, isoleucine, or valine is to be imported into the cells as a sole nitrogen source for amino acids and protein synthesis within the cells. However, arginine, ornithine, isoleucine, and valine are not the only nitrogen source that can be used and RocCE are not necessary when the cells use nitrogen sources other than arginine, ornithine, isoleucine, and valine. As the prior art indicates, *B. subtilis* cells having inactivated *rocR* or *sigL* do grow when other nitrogen sources are used; the necessary amino acids are biosynthesized by the cells and protein synthesis is not affected (see Debarbouille et al., cited by the applicant; p. 9092, column 2, third full paragraph, p. 9095, column 1, teaching using alanine, NH₄,

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aminobutyrate, urea, or nitrate as a nitrogen source for *B. subtilis* having inactivated *sigL*). Based on the teachings in the art as a whole, one of skill in the art would have known to use the proper nitrogen sources for *B. subtilis* cells having inactivated *rocR* or *sigL* such that protein synthesis in these cells is not affected.

For the reasons set forth above, the applicant's arguments are not found persuasive and the rejection is maintained.

Conclusion

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action (specifically, the inclusion of the new claims 8-15 in the 103 rejection). Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Primary Examiner, Art Unit 1633